REMARKS

This Preliminary Amendment is submitted together with a Continued Prosecution Application Request. The Official Action dated November 22, 2000 and the Advisory Action dated April 23, 2001 have been carefully considered, and the Examiner's detailed comments are acknowledged and appreciated. Accordingly, the changes presented herewith, taken with the following remarks, are believed to be sufficient to place the present Continued Prosecution Application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 51 and 54 are canceled. Claims 1 and 19 are amended to clarify the transfecting step in accordance with the teachings of the specification and to recite that the enhancer element is "upstream of the promoter" in the construct as previously set forth in these claims and in claim 51. Claim 46 is amended to recite that the promoter is "upstream of the gene" and that the cell is transfected with the DNA construct "upstream of the promoter" as previously set forth in this claim and in claim 51. Claim 44 is amended to include limitations from claim 54. Claims 5, 8, 23, 27, 30 and 34 are amended to delete the proviso clause, and claims 8 and 10 are amended to clarify the recitation of the nucleotide sequences set forth therein. Claims 27 and 30 are amended to clarify that the enhancer element is incorporated with the structural gene by fusion, in accordance with the teachings throughout the specification and the pending method claims. Finally, claims 47-50 are amended to correspond with the claims from which they respectively depend. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

In the Official Action, claims 1, 2, 19-21, 39, 40 and 44-52 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention. With respect to claims 1, 19 and 46, the Examiner asserted that the enhancer element must be incorporated into the genome upstream of the promoter of the DNA construct recited in the claim. With respect to claims 44 and 45, the Examiner asserted that the specification does not teach how to use a DNA construct that does not comprise any gene. In the Advisory Action, the Examiner asserted that the specification only describes transfection of recombinant constructs already including the enhancer element.

This rejection is traversed with respect to present claims 1, 2, 19-21, 39, 40, 44-50 and 52. More particularly, claims 1 and 19 recite, inter alia, the steps of providing the DNA construct with an enhancer element upstream of the promoter and transfecting the eukaryotic host cell to incorporate the DNA construct. Claim 46 recites the steps of, inter alia, providing a cell comprising the gene and a promoter "upstream of the gene", and transfecting the cell with a DNA construct comprising an enhancer element "upstream of the promoter". Finally, claim 44 recites that the isolated DNA construct comprises a structural gene, a promoter and six repeats of an enhancer. It is therefore submitted that claims 1, 19, 44 and 46 are enabled by the present specification, whereby the rejection of claims 1, 2, 19-21, 39, 40, 44-50 and 52 under 35 U.S.C. §112, first paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 1, 2, 5, 7-11, 15-17, 19-21, 23-26, 34-36, 39-42 and 44-54 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. As will be set forth in detail below, it is believed that the claims as presented herein are definite in accordance with the requirements of 35 U.S.C. §112, second paragraph. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More specifically, Claims 1, 2, 19-21, 39-42 and 46-52 were asserted to be indefinite because the arrangement of the genetic elements, i.e., the enhancer, promoter and structural

gene, were not specified. As noted above, claims 1, 19 and 46 now recite that the promoter is upstream of the structural gene and that the enhancer element is upstream of the promoter. It is therefore submitted that claims 1, 2, 19-21, 39-42, 46-50 and 52 are definite and that the rejection has been overcome.

Claims 1, 2, 39, 40 and 51 were asserted to be indefinite in the recitation of the step of "transfecting the eukaryotic host cell with six copies of an enhancer element" because it was unclear whether only six copies of element are used to perform the transfection or six copies of the element actually go into the cell and are incorporated into the genome of the cell. Claim 1 now recites the steps of providing the DNA construct with six copies of an enhancer element upstream of the promoter and transfecting the eukaryotic host cell to incorporate the DNA construct. It is therefore submitted that claim 1, and claims 2, 39, and 40 dependent thereon, are definite and that the rejection has been overcome.

Claims 5, 7-11, 15-17, 23-26, 34-36, 44, 45, 50, 53 and 54 were asserted to be indefinite in reciting the proviso that the nucleotide sequence is not the nucleotide sequence SEQ ID NO:1, as it was unclear how "consists essentially of the nucleotide sequence TTCTGAGAA" could be construed to encompass the 52 nucleotide sequence of SEQ ID NO:1. The Examiner is correct that the recitation in claims 5, 8, 23, 27, 30 and 34 of an enhancer element "consisting essentially of the nucleotide sequence TTCTGAGAA" does not include or encompass the 52 nucleotide sequence of SEQ ID NO:1. Accordingly, these claims have been amended to delete the proviso which recited that the nucleotide sequence is not the sequence of SEQ ID NO:1. It is therefore submitted that claims 5, 7-11, 15-17, 23-26, 34-36, 44, 45, 50 and 53 are definite and that the rejection has been overcome.

Claims 10 and 17 were asserted to be indefinite in the recitation that the enhancer element comprises at least one copy of the nucleotide sequence SEQ ID NO:1 as claim 8, from which they depend, carried the proviso that the nucleotide sequence is not the

nucleotide sequence SEQ ID NO:1. Claim 8 recites an expression vector comprising, inter alia, six enhancer elements, wherein at least one of the enhancer element consists essentially of the nucleotide sequence TTCTGAGAA and the remaining enhancer elements comprise the nucleotide sequence TTCTGAGAA. On the other hand, claim 10 recites that at least one of the remaining enhancer elements is the nucleotide sequence SEQ ID NO:1. As these claims consistently define the enhancer element, it is believed that claims 8 and 10, and claim 17 which depends from claim 10, are definite, and that the rejection has been overcome.

Claims 19-21 and 49 were asserted to be indefinite in their recitation of "transfecting the eukaryotic host cell with at least one enhancer element" because it is unclear if only at least one enhancer element is used to perform the transfection or if only at least one enhancer element actually goes into the cell and is incorporated into the genome of the cell. Claim 19 now recites the steps of providing the DNA construct with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA upstream of the promoter and transfecting a eukaryotic host cell wherein transcription can occur to incorporate the DNA construct. It is therefore submitted that claim 19 and claims 20, 21 and 49 dependent thereon are definite and that the rejection has been overcome.

It is therefore submitted that all of claims 1, 2, 5, 7-11, 15-17, 19-21, 23-26, 34-36, 39-42, 44-50, 52 and 53 are definite and that the rejection under 35 U.S.C. §112, second paragraph, has been overcome. Reconsideration is respectfully requested.

Claims 19, 20, 49 and 54 were rejected under 35 U.S.C. §102(b) as being anticipated by Yoon et al (1990). In response to the arguments set forth in Applicants' previous Amendment, the Examiner asserted that the rejected claims read on the method disclosed by Yoon et al because the constructs described by Yoon et al include the nucleotide sequence TTCTGAGAA while the instant claims recite transfecting a host cell with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA. The Examiner

acknowledged that one skilled in the art would not expect a piece of DNA consisting of only these nine nucleotides to incorporate upstream of the promoter, but the Examiner asserted that, once incorporated into the proper location, some space in between the promoter and the enhancer element is to be expected, and the constructs described by Yoon et al are of such a type wherein the enhancer element is not directly adjacent to the promoter, rather there are a number of nucleotides that act as spacers between the enhancers and the promoter. The Examiner further asserted that Yoon et al need not teach a segment smaller than the 50 bp segment set forth as SPI-GHRE because the segment that they used included the nucleotide sequence recited in the claim despite the fact that they included some flanking sequences in their constructs. The Examiner concluded that it is not necessary that Yoon et al recognize or teach the minimal sequence that will function as an enhancer because no matter how long the piece of DNA is initially, once it is incorporated into the DNA construct it necessarily becomes flanked by other nucleotides.

However, as will be set forth in detail below, Applicants submit that the methods defined by claims 19, 20 and 49 are not anticipated by Yoon et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More specifically, claim 19 is directed to an *in vitro* method of enhancing the transcription of a gene in a DNA construct comprising a structural gene and a promoter upstream of the structural gene. The method comprises providing the DNA construct with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA upstream of the promoter, transfecting a eukaryotic host cell wherein transcription can occur to incorporate the DNA construct, and exposing the DNA construct to a hormone selected from the group consisting of lactogenic hormones, somatogenic hormones and mixtures thereof.

Anticipation under 35 U.S.C. §102 requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1

U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). As the Examiner has acknowledged, Yoon et al neither teach nor recognize an enhancer element consisting of the nucleotide sequence TTCTGAGAA. Moreover, the Examiner acknowledges that the skilled artisan would not expect a piece of DNA consisting of the nucleotide sequence TTCTGAGAA to incorporate upstream of a promoter as recited in claim 19. Thus, Yoon et al do not teach any method which comprises providing a DNA construct with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA upstream of the promoter and transfecting a eukaryotic host cell with the DNA construct , as required by claim 19. Thus, Yoon et al do not disclose each element of claim 19 and therefore do not anticipate claim 19 under 35 U.S.C. §102.

While the construct described by Yoon et al may include an enhancer element of the nucleotide sequence TTCTGAGAA, Yoon et al do not teach a method wherein a DNA construct is provided with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA upstream of the promoter and is then incorporated into the eukaryotic host cell by transfection. Rather, Yoon et al disclose the use of the 50 bp segment. Any similarity in the construct of Yoon et al and the construct resulting from claim 19 does not teach the method of claim 19 which includes, inter alia, the steps of providing a DNA construct with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA upstream of the promoter and transfecting the eukaryotic host cell with the DNA construct.

It is therefore submitted that the methods defined by claim 19, and claims 20 and 49 dependent thereon, are not anticipated by Yoon et al, and that the rejection under 35 U.S.C. §102 has been overcome. Reconsideration is respectfully requested.

Claims 27-32 were rejected under 35 U.S.C. §103(a) as being unpatentable over Lindquester et al (1989). In response to the arguments presented in Applicants' previous

Amendment, the Examiner asserted that one of skill in the art would have anticipated a reasonable expectation of success for making the expression vector and host cell comprising the expression vector because only standard molecular biology techniques are required and one of ordinary skill in the art would have been motivated to use the nucleotide sequence disclosed by Lindquester et al to construct an expression vector in a host cell comprising the expression vector in order to produce tropomyosin in culture for further study of the protein and the regulatory sequences driving the expression of the protein. The Examiner asserted that the vector would have necessarily contained the enhancer element present in the gene and the hormone responsiveness of the element is an inherent property of the element.

However, as will be set forth in detail below, Applicants submit that the expression vectors defined by claims 27 and 30 are nonobvious over and patentably distinguishable from the teachings of Lindquester et al. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More specifically, as defined by claim 27, the expression vector comprises a structural gene encoding a protein, a promoter and at least one enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA. The enhancer element is incorporated with the structural gene by fusion. Claim 30 is directed to a DNA comprising a promoter, a structural gene, and at least one enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA. The enhancer element is incorporated with the structural gene by fusion.

In contrast, Lindquester et al describe their study of avian tropomyosin gene expression. As noted by the Examiner, Lindquester et al disclose that the avian tropomyosin gene includes the sequence TTCTGAGAA located in one of the introns, specifically at position 18602 of Figure 1 on page 2105, and that a genomic clone containing tropomyosin gene was isolated from a quail DNA genomic library.

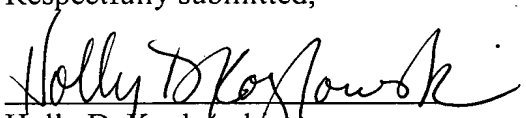
However, Applicants find no teaching or suggestion by Lindquester et al of an expression vector as defined in claim 27 or a DNA as defined in claim 30 comprising, inter alia, a structural gene, a promoter, and at least one enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA, particularly wherein the enhancer element is incorporated with the structural gene by fusion. Moreover, the mere teaching by Lindquester et al of the avian tropomyosin gene including the nucleotide sequence TTCTGAGAA, without further teaching, suggestion or recognition of the ability of the nucleotide sequence to act as an enhancer element, provides no teaching or suggestion to one of ordinary skill in the art to produce either an expression vector or a DNA as recited in claims 27 and 30, wherein the enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA is incorporated with the structural gene by fusion.

References relied upon to support a rejection under 35 U.S.C. §103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public, *In re Payne*, 203 U.S.P.Q. 245 (CCPA 1979). Lindquester's disclosure of the avian tropomyosin gene including the nucleotide sequence TTCTGAGAA does not place either the expression vector of claim 27 or the DNA of claim 30 comprising, inter alia, an enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA incorporated with the structural gene by fusion in the possession of the public. Similarly, Lindquester et al's disclosure of the avian tropomyosin gene including the nucleotide sequence TTCTGAGAA does not provide an enabling disclosure of either the expression vector of claim 27 or the DNA of claim 30 which comprise, inter alia, the enhancer element incorporated with the structural gene by fusion. Thus, Lindquester et al do not support a rejection of claims 27-32 under 35 U.S.C. §103. It is therefore submitted that the expression vector as defined by claims 27-29 and the DNA defined by claims 30-32 are nonobvious over and patentably

distinguishable from Lindquester et al, whereby the rejection under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the Examiner's rejections under 35 U.S.C. §§ 102, 103 and 112, first and second paragraphs, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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VERSION WITH MARKINGS SHOWING CHANGES MADE

Claims 1, 5, 8, 10, 19, 23, 27, 30, 31, 34, 44 and 46-50 are amended as follows:

1. (Fifth Amendment) An in vitro method of enhancing the transcription of a gene in a DNA construct when the DNA construct is incorporated into the genome of a eukaryotic host cell, said DNA construct comprising a structural gene for a desired protein or polypeptide and a gene promoter upstream of the structural gene, the method comprising the steps of:

(a) providing the DNA construct with six copies of an enhancer element upstream of the promoter;

(b) transfecting the eukaryotic host cell [with six copies of an enhancer element upstream of the promoter] to incorporate the DNA construct, and

(c)[(b)]exposing the DNA construct to a hormone selected from the group consisting of lactogenic hormones, somatogenic hormones and mixtures thereof;

wherein the enhancer element comprises the nucleotide sequence TTCTGAGAA, with the proviso that the nucleotide sequence does not contain the DNA sequence of nucleotide sequence SEQ ID NO:1, and wherein the enhancer element is responsive to both lactogenic hormones and somatogenic hormones.

5. (Fourth Amendment) An enhancer element which when used in a DNA construct for transfection of a eucaryotic host cell is responsive to hormonal stimuli, said enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA, [with the proviso that said nucleotide sequence is not the DNA sequence of SEQ ID NO:1, and that] wherein the enhancer element is responsive to both lactogenic hormones and somatogenic hormones.

8. (Third Amendment) An expression vector comprising a structural gene encoding a desired protein or polypeptide and a promoter, wherein the vector further comprises six [copies of an] enhancer elements, and further wherein at least one of the enhancer elements consists [element consisting] essentially of the nucleotide sequence TTCTGAGAA and the remaining enhancer elements comprise the nucleotide sequence TTCTGAGAA.

10. (Fourth Amendment) The expression vector according to claim 9, wherein at least one of the remaining [said] enhancer elements is [element comprises at least one copy of] the nucleotide sequence SEQ ID NO:1.

19. (Third Amendment) An in vitro method of enhancing the transcription of a gene in a DNA construct comprising a structural gene and a promoter upstream of the structural gene, the method comprising;

(a) [placing] providing the DNA construct with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA upstream of the promoter [in an eukaryotic host cell wherein transcription can occur];

(b) transfecting [the] a eukaryotic host cell wherein transcription can occur to incorporate the DNA construct [with at least one enhancer element consisting of the nucleotide sequence TTCTGAGAA upstream of the promoter], and

(c) exposing the DNA construct to a hormone selected from the group consisting of lactogenic hormones, somatogenic hormones and mixtures thereof.

23. (Third Amendment) An enhancer element responsive to a hormone selected from the group consisting of lactogenic hormones, somatogenic hormones and mixtures

thereof when the enhancer element is used in a DNA construct for transfection of a eukaryotic host cell; wherein the enhancer element consists essentially of the nucleotide sequence TTCTGAGAA[, with the proviso that the nucleotide sequence is other than the nucleotide sequence of SEQ ID NO:1].

27. (Third Amendment) An expression vector comprising a structural gene encoding a protein, a promoter, and at least one enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA, [with the proviso that the nucleotide sequence is other than the nucleotide sequence SEQ ID NO:1] wherein the enhancer element is incorporated with the structural gene by fusion.

30. (Twice Amended) A DNA comprising a promoter, a structural gene, and at least one enhancer element consisting essentially of the nucleotide sequence TTCTGAGAA, [with the proviso that the nucleotide sequence is other than the nucleotide sequence SEQ ID NO:1] wherein the enhancer element is incorporated with the structural gene by fusion.

31. (Twice Amended) A DNA according to claim 30, comprising from one to six enhancer elements.

34. (Third Amendment) An in vitro method of enhancing the transcription of a gene in a DNA construct comprising a structural gene, a promoter upstream of the structural gene, and at least one enhancer upstream of the promoter; the method comprising

placing the DNA construct in an environment wherein transcription can occur; and

exposing the DNA construct to a hormone selected from the group consisting of lactogenic hormones, somatogenic hormones and mixtures thereof;

wherein the enhancer element consists essentially of the nucleotide sequence TTCTGAGAA[, with the proviso that the nucleotide sequence is other than the nucleotide sequence SEQ ID NO:1].

44. (Twice Amended) An isolated DNA construct comprising a structural gene, a promoter and six repeats of an enhancer, wherein the enhancer consists essentially of the sequence TTCTGAGAA.

46. (Twice Amended) An in vitro method of enhancing the transcription of a gene, the method comprising the steps of:

(a) providing a cell comprising the gene and a promoter upstream of the gene,

(b) transfecting the cell with a DNA construct comprising at least one copy of the nucleotide sequence TTCTGAGAA upstream of the promoter, and

(c) exposing the DNA construct to prolactin.

47. (Amended) An in vitro method according to claim 46, wherein the DNA construct comprises [comprising the step of providing] multiple copies of the nucleotide sequence TTCTGAGAA.

48. (Twice Amended) An in vitro method according to claim 47, wherein the DNA construct comprises [comprising the step of providing] six copies of the nucleotide sequence TTCTGAGAA.

49. (Amended) An in vitro method according to claim 19, wherein the transfecting step [of placing the DNA construct in an environment wherein transcription can

occur] comprises transfecting [an] the eukaryotic cell with a plasmid comprising the DNA construct.

50. (Amended) An in vitro method according to claim 34, wherein the transfecting step [of placing the DNA construct in an environment wherein transcription can occur] comprises transfecting [an] the eukaryotic cell with a plasmid comprising the DNA construct.